

REMARKS

The Office Action

Claims 1-7 are pending. Claims 1-7 stand rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement, with the Office citing Beck et al. (U.S. Patent Pub. No. 2004/0146495; hereafter “Beck”), Williams et al. (“Intravenous Secretin for Autism Spectrum Disorder,” *Cochrane Database of Systematic Reviews*, Issue 3. Art. No.: CD003495 (2005); hereafter “Williams”), Lam et al. (“Multiple Actions of Secretin in the Human Body,” *Int. Rev. Cytol.* 265: 159-190 (2008), abstract only; hereafter “Lam”), Herlihy (Repligen Corp. Press Release, “Repligen Reports Initial Clinical Data for Secretin in Schizophrenia,” Feb. 4, 2005; hereafter “Repligen (2005)”), Herlihy (Repligen Corp. Press Release, “Repligen Licenses Patent Rights for Treatment of Bipolar Disorder,” Mar. 31, 2009; hereafter “Repligen (2009)”), Freedman et al. (U.S. Patent Pub. No. 2009/0088404; hereafter “Freedman”), Tedford et al. (U.S. Patent Pub. No. 2006/0035889; hereafter “Tedford”), Levitt et al. (U.S. Patent Pub. No. 2007/0072233; hereafter “Levitt”), and Pardee et al. (U.S. Patent Pub. No. 2009/0104171; hereafter “Pardee”). Claims 1-7 stand further rejected under 35 U.S.C. § 112, second paragraph, for indefiniteness. Claims 1-4 stand rejected under 35 U.S.C. § 102 for anticipation by McMichael (U.S. Patent No. 6,020,314), and claims 1-7 stand rejected under 35 U.S.C. § 103 for obviousness over McMichael in view of Renshaw (U.S. Patent Pub. No. 2002/0019364), Ford (“The Use of Anticonvulsants in Posttraumatic Stress Disorder: Case Study and Overview,” *J. Trauma. Stress* 9: 857-863 (1996)), and Nishizono (U.S. Patent No. 4,443,469). These rejections are discussed in detail below.

Amendments to the Claims

Claim 1 has been amended to specify that the method is “for ameliorating bipolar disorder in an individual in need thereof” and to specify that the amount of secretin is “sufficient to ameliorate bipolar disorder.” Support for this amendment is on page 5, lines 16 – 29 in the specification. Claim 2 has been amended to specify that “per

kilogram of bodyweight” relates to the individual of claim 1 and to be consistent with the amendments to claim 1. Claim 6 has been amended to specify that “administering” relates to the individual of claim 1. Claim 7 has been amended to delete duplications. Claims 4 and 5 are cancelled. No new matter is added by these amendments.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 1-7 stand rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. As the basis for this rejection, the Office states that treatments for amygdala-associated disorders remain unpredictable, as indicated by Beck, Williams, Lam, Repligen (2005), and Repligen (2009); that cures or preventions for amygdala-associated disorders remain unknown, as indicated by Freedman, Tedford, Levitt, and Pardee; that the specification provides limited guidance to practice the invention; and that the specification lacks an example of a working embodiment. The Office concludes that undue experimentation would be required to determine the therapeutic effect of secretin for treating amygdala-associated disorders. Applicants traverse the rejection.

Amended claim 1, from which all other claims depend, recites:

1. A method for ameliorating bipolar disorder in an individual in need thereof, said method comprising administering an amount of secretin sufficient to ameliorate bipolar disorder in said individual.

The amended claim now focuses on bipolar disorder, and, in addition, is directed to ameliorating this disorder. Accordingly, the amended claim excludes preventive treatment and no longer requires that the subject be “cured.” This claim is enabled by the specification.

As stated in M.P.E.P. § 2164, “[t]he purpose of the requirement that the specification describe the invention in such terms that one skilled in the art can make and use the claimed invention is to ensure that the invention is communicated to the interested public in a meaningful way.” In making a determination on enablement, M.P.E.P. § 2164.04 requires:

A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as being in compliance with the enablement requirement ..., unless there is a reason to doubt the objective truth of the statements contained therein... (emphasis added)

Furthermore, the Office is required to “back up assertions of its own with acceptable evidence or reasoning which is *inconsistent* with the contested statement.” (M.P.E.P. § 2164.04; emphasis added). Such evidence or reasoning has not been provided by the Office to support the rejection of the amended claims.

The specification provides ample teaching for one skilled in the art to practice the full scope of the amended claims without undue experimentation. The specification states that the present invention provides methods for treating patients suffering from bipolar disorder by administering secretin (page 6, lines 13 – 15). Further, the specification provides suitable routes for administering secretin (page 7, lines 7 – 14), dose ranges for secretin (page 8, lines 21 – 28), and a description of bipolar disorder (page 11, lines 12 – 18).

The enabling nature of the specification is discussed in the accompanying declaration of Dr. Yurgelun-Todd, which further provides human experimental data in support of enablement. In the Declaration (¶ 2), Dr. Yurgelun-Todd opines that it is reasonable to conclude that secretin would be effective in treating a bipolar disorder, based on Dr. Yurgelun-Todd’s experimental observations that secretin modulates amygdalar activation in healthy patients (page 12, line 12 – page 18, line 10 of the specification), the knowledge that abnormal amygdalar function is implicated in bipolar disorder (page 1, line 14 – page 2, line 21 of the specification), and experimental observations of improvement in bipolar patients treated with secretin (¶¶ 4 – 8 in the Declaration).

As stated in the Declaration (¶ 3), the specification provides experiments on functional magnetic resonance imaging (fMRI) of healthy control patients (page 12, line 12 – page 18, line 10). These fMRI experiments demonstrate that secretin alters

amygdala responsiveness to affective stimuli. The specification also teaches that abnormalities of the amygdalar-frontal circuit have been implicated in a variety of behavioral and psychiatric disorders, including bipolar disorder (page 1, line 14 – page 2, line 21). Thus, the specification provides direction and guidance to practice the invention as currently claimed, as well as a working example of the neurophysiological effects of secretin.

Further, as reported in the Declaration (§ 4), Dr. Yurgelun-Todd has conducted a double-blind crossover placebo-controlled study to examine whether the administration of secretin results in mood stabilization. This study was conducted in eight male patients aged 18-40 years and meeting the diagnostic criteria for Bipolar I or II disorder (DSM-IV). The patients, who were in a mildly depressed phase of the illness during the study, were allowed to continue their current treatment as usual pharmacotherapy. They were administered clinical ratings, mood scales, and select neurocognitive measures designed to assay specific relevant domains both before and four hours following treatment with secretin or placebo. Although the investigation included a double-blind placebo controlled visit, “placebo” in this case referred to the patient’s standard pharmacotherapy with no secretin. Patients were administered a single dose of secretin equivalent to 1.0 µg/kg intravenously. This treatment is generally described in the specification at pages 6-10. Vital signs were monitored following drug administration. As this was a double-blind study, the drug/placebo bags were randomized. Various clinical rating scales were administered to the patients, which included the Young Mania Rating Scale (YMRS), the Montgomery-Asberg Depression Rating Scale (MADRS), the Hamilton Depression Scale (HAM-D) scores, the Barratt Impulsivity Scale (BIS), the Profile of Mood States (POMS), the State-Trait Inventory (STAI), the Clinical Global Impression for Bipolar Patients (CGI-BP), and the Positive and Negative Affect Scale (PANAS). All patients were scanned using fMRI both before and after administration of the placebo or secretin. Baseline scanning included structural MRI and fMRI scanning on a 3T magnet. Following the first scanning session, patients were administered either placebo (saline) or a single infusion of secretin via an infusion. One hour after drug administration, patients

underwent the second fMRI scanning protocol and were then re-assessed on the clinical rating scales. Within two weeks, patients repeated these procedures for study visit two and were administered either saline or secretin, whichever they did not receive in study visit one. During the fMRI part of the protocol, patients completed two challenge paradigms that included the presentation of happy, sad, fearful, and neutral faces, as well as more cognitively based tasks requiring the inhibition of overlearned responses, such as the Stroop test.

As stated in the Declaration (§ 5), patients in the study showed improvement when assessed by the Positive and Negative Affect Scale test. As shown in Figures 1 and 2, negative symptoms were reduced after both placebo and secretin injection, where responses to the negative affect subscale after secretin injections suggested a trend toward significant improvement ($p = 0.064$) (Declaration, Figure 1). Responses to the positive affect subscale were essentially unchanged for the placebo injection but did appear reduced following secretin injection (Declaration, Figure 1). Individual responses to the negative symptom portion showed that administration of a single dose of secretin produced some reduction of negative symptoms in four out of the six patients with bipolar disorder (Declaration Figure 2). As stated by Dr. Yurgelun-Todd, it is not surprising that only a subset of patients reported an observable clinical effect, as most treatment interventions have shown effects on limited patient subgroups.

As stated in the Declaration (§ 7), patients in the study also showed improvement when assessed by the Stroop Color Word Task test. As shown in Figure 3, patients were administered the Stroop Color Word Task test, which measures cognitive inhibition. The patients receiving secretin demonstrated improved performance on all three conditions of color naming, word reading, and interference following the secretin injection relative to baseline. However, only performance on the word reading condition reached statistical significance ($p = 0.025$). In contrast, following the placebo injection, no differences in performance were detected for any condition relative to baseline.

As stated in the Declaration (§ 8), fMRI experiments were conducted as part of the study. As shown in Figures 4 and 5, patients were scanned using fMRI. The fMRI

findings showed that secretin alters brain activation in multiple brain regions. In particular, administration of secretin increased amygdalar activation in bipolar patients, compared to administration of placebo. Along with the other structures identified, including the superior temporal gyrus and the cingulate gyrus, the amygdala is considered a key structure in emotional processing, and these findings suggest that secretin aids in the normalization of amygdalar response to emotional stimuli in a variety of conditions, in this case, bipolar disorder. Thus, the claimed method has been demonstrated to be effective in ameliorating bipolar disorder.

Moreover, none of the references cited by the Office calls into question the efficacy of the invention. Many of the references do not discuss bipolar disorder at all. For example, Beck and Williams discuss treatments for autism. Lam provides a general summary about the actions of secretin in the human body. Repligen (2005) and Levitt discuss treatments for schizophrenia. Tedford discusses treatments for methamphetamine addiction. As these references do not discuss bipolar disorder, they are not relevant to the enablement of the amended claims.

Repligen (2009), Freedman, and Pardee do discuss treatments for bipolar disorder, but none of these references mentions secretin. For example, Repligen (2009) discusses oral formulations of uridine; Freedman discusses S-methyladenosylmethionine; and Pardee discusses a nutritional supplement that includes trimethylglycine, L-tryptophan, L-acetyl carnitine, and vitamin B6. As these references disclose other treatments for bipolar disorder, they actually support the enablement of the present application by suggesting that treatment of bipolar disorder is possible.

Further, Applicants acknowledge that Repligen (2009) states that current therapies for bipolar disorder are ineffective. As stated in the Declaration (§ 9), Dr. Yurgelun-Todd has reviewed Repligen (2009). This reference discusses a license agreement for intellectual property owned by The McLean Hospital Corporation, the assignee of this application. As Dr. Yurgelun-Todd notes, Repligen (2009) states that “current therapies [for bipolar disorder] are ineffective and result in numerous side effects” but further explains that while “several therapies are approved for the treatment of bipolar disorder,

many individuals are unable to tolerate treatment-related side effects.” Thus, Repligen (2009) indicates that treatments are available for bipolar disorder. Dr. Yurgelun-Todd also states that Repligen (2009) corroborates the observation (as discussed in ¶ 5 in the Declaration) that not all therapies work in all patients and that most therapies are effective on patient subgroups. Thus, Repligen (2009) is consistent with Applicants’ position and does not call into question the effectiveness of secretin for ameliorating bipolar disorder.

In summary, the specification teaches how to treat bipolar disorder with secretin, Applicants have provided data on the efficacy of this treatment, and nothing in the cited references calls into question the enablement of the amended claims. This rejection may be withdrawn.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 1-7 stand rejected under 35 U.S.C. § 112, second paragraph, for indefiniteness on a number of grounds. These bases for rejection have been met as follows.

Applicants have amended independent claim 1 to specify that the “disorder associated with the amygdala” is bipolar disorder. Claim 1 has also been amended to recite that the amount of secretin is “sufficient to ameliorate bipolar disorder.” By this amendment, the “therapeutic effect” is explicitly recited in the claim.

Applicants have amended claim 2 to specify that “per kilogram of bodyweight” refers to the individual of claim 1 and claim 6 to specify that “administering” relates to the individual of claim 1, as requested by the Office. Claim 4 has been cancelled, rendering the rejection of that claim moot.

Finally, Applicants disagree with the Office’s position that “clinical unit” is indefinite. The Office states that the term “is not supported by a definition of the term in the specification” and “is not accepted in the art as referring to any particular amount,” but the specification and cited art refute this position. First, the specification defines a clinical unit, stating “The clinical unit is as defined by Jorpes et al. (1966)” and “For

SecreFlo™ [secretin], 1 CU is equivalent to 0.2 µg” (page 8, lines 24 – 26). Second, Williams, a reference cited by the Office in connection with the enablement rejection, is illustrative of the fact that the term “CU” is art recognized as a dosage unit of secretin. Of the fourteen studies reviewed in Williams, more than ten report the dosage of secretin in units of “CU/kg” (see pages 8 and 25 – 32). Thus, the term “clinical unit” is definite, and this basis for the rejection should be withdrawn.

Rejections under 35 U.S.C. § 102

Claims 1-4 are rejected under 35 U.S.C. § 102 as being anticipated by McMichael. Claim 4 has been cancelled. Applicants have amended independent claim 1, from which claims 2 and 3 depend, to specify that the individual suffers from bipolar disorder. McMichael does not mention bipolar disorder and, therefore, is not anticipatory to the present claims.

Rejections under 35 U.S.C. § 103

Claims 1-7 are rejected under 35 U.S.C. § 103 as being obvious over McMichael in view of Renshaw, Ford, and Nishizono, to the extent that irritability is a symptom being treated. Amended claim 1 is directed to ameliorating bipolar disorder. As none of the cited references teaches or suggests a treatment for bipolar disorder, no combination of the cited art can teach or suggest the present claims. This rejection should also be withdrawn.

Information Disclosure Statement

The reference “Repligen Corporation. “SecreFlo™ (Secretin) for Injection.” (2002)” was provided with the Information Disclosure Statement filed on May 2, 2007. As noted on the initialed PTO Form-1449 of April 17, 2009, the Examiner did not consider this reference on the basis that page numbers were not included in the citation. Applicants note that this reference does not have page numbers, and further that all pages

of the reference were submitted to the Office. Applicants request that the Examiner consider this reference and return an initialed Form-1449 with the next Action.

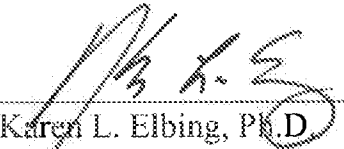
CONCLUSION

Applicants submit that the claims are in condition for allowance, and such action is respectfully requested. Enclosed is a Petition to extend the period for replying to the Office action for **three** months, to and including November 4, 2009. Applicants authorize the charge of \$555.00 to Deposit Account 03-2095 for the required fee.

If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: 04 November 2009



Karen L. Elbing, Ph.D.
Reg. No. 35,238

Clark & Elbing LLP
101 Federal Street
Boston, MA 02110
Telephone: 617-428-0200
Facsimile: 617-428-7045